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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/74658 A1

(54) Title: USE OF DRUG-LOADED NANOPARTICLES FOR THE TREATMENT OF CANCERS

(57) Abstract: The present invention relates to the use of drug-loaded nanoparticles for preparing a medicament for the treatment of cancer, particularly for the treatment of cancer in the brain, even more particularly for the treatment of brain cancer in humans. The invention also relates to a process for the treatment of brain cancer, particularly for the treatment of brain cancer in humans by administering an effective amount of nanoparticles containing a substance which has effect in the cancer treatment or has immunosuppressive effects.

Use of Drug-Loaded Nanoparticles for the Treatment of Cancers

The present invention relates to the use of drug-loaded nanoparticles for preparing a medicament for the treatment of cancer, particularly for the treatment of cancer in the brain, even more particularly for the treatment of brain cancer in humans. The invention also relates to a process for the treatment of brain cancer, particularly for the treatment of brain cancer in humans, by administering an effective amount of nanoparticles containing a substance which has effect in the cancer treatment or has immunosuppressive effects.

It was reported in the U. S. Patent Application S. N. 08/203,326 and the parallel International Patent Application No. PCT/EP 95/00724 (corresponding to WO 95/22963) that drugs may be delivered to the body of mammals, particularly to the body of humans, and may be transported across the blood brain barrier (furtheron referred to as "bbb") by means of nanoparticles to which drugs are complexed (incorporated, adsorbed or absorbed) and which are surrounded by a coating made of an appropriate surfactant. A similar teaching can be found in the pending International Patent Application No. PCT/EP 97/03099. It was taught in both of said applications that the drug may be an immunosuppressive or anticancer agent. As the appropriate surfactant, there were taught a number of generally and commercially available surfactants as, for example, Polysorbate ^{R} 80 or Tween ^{R} 80.

It is general knowledge that the non-invasive treatment of cancers in the brain of mammals, particularly in the brain of humans has to rely on very small amounts of immunosuppressive or anticancer medicaments or drugs which are transported to the desired target, i. e. the tumor in the brain. In particular, anticancer agents known to have a high effect in the anticancer treatment do not at all or do not in a sufficiently effective amount pass the blood brain barrier (bbb) and are effective only when delivered directly into the brain. Such a delivery step, however, means a delivery into the skull at a suitable point which is a very complicated and sometimes risky surgery step.

The term "blood brain barrier " (bbb) as used herein refers to the bbb in the narrower sense, i. e. in the sense this term is used usually by a person skilled in the medical field, as well as to the blood spinal barrier and blood retina barrier.

It was now surprisingly found that nanoparticles prepared in accordance with teachings of the prior art, particularly of the above two Patent Applications, may be loaded with a substance having effect in the treatment of cancers, particularly having effect in the treatment of cancers in the brain, for example in humans, in an effective amount and may then be coated with a suitable surfactant so as to allow that drug-loaded nanoparticles to pass across the bbb and to deliver the effective drug to the site where it may exhibit its anticancer and/or immunosuppressive activity. It was particularly found that, by a suitable selection of the combination drug/surfactant, an effective use of such nanoparticles loaded with the drug and coated with a surfactant in the treatment of cancers, particularly of cancers in the brain, may be proviced.

Hence, the invention relates to the use of nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within or on said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, for the manufacture of a medicament for the treatment of cancer in said mammal.

In a preferred embodiment of the present invention, the treatment of cancer is a treatment of cancer in the brain. In an even more preferred embodiment, the brain cancer treatment is a treatment to a human. The terms "cancer" and "tumor(s)" are used in the description and claims in a synonymous manner.

The nanoparticles used in the present invention for the cancer treatment are nanoparticles which mainly consist of three major components, i. e. the polymeric material which is used to form a wall either incorporating the drug or physiologically effective substance(s) or containing said substance(s) adsorbed or absorbed thereto, e. g. onto its surface; the physiologically effective substance or substances contained within or on said nanoparticle; and a stabilizer or more than one stabilizer allowing the passage of said nanoparticle across the bbb.

Although there are basically no limitations with respect to any of the above three components and their combinations, as long as they allow the achievement of the intended goal, the present invention comprises as one of the preferred embodiments the use of said nanoparticles, wherein said nanoparticles comprise particles of said polymeric material having a diameter of below 1,000 nm, preferably of from 1 to 1,000 nm.

In a further preferred embodiment, the invention relates to the use of said nanoparticles, wherein said polymeric material the nanoparticles are consisting of is selected from the group consisting of polyacrylates, polymethacrylates, poly-cyanoacrylates, polyacrylamides, polylactates, polyglycolates, polyanhydrates, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacroöein, polyglutaraldehydes and derivatives, copolymers and mixtures thereof. There is of course no limit with respect to the specific material of the nanoparticles, as long as the material used allows or even promotes the successful transport to and passage across the bbb of the physiologically effective substanc or substances.

In accordance with the present use of the nanoparticles according to the invention, there is/are provided within or on said nanoparticles (incorporated, absorbed and/or adsorbed) one or more substances which are physiologically effective in the treatment of cancer upon

delivery to a mammal. The substances may be a single substance or may be two or even more substances which may act on the human body on a separate route or on a combined route or even synergistic route.

In a preferred use according to the present invention, said physiologically effective substance(s) to be delivered to said mammal comprise(s) one or more chemotherapeutic agent(s) for the cancer treatment, particularly for the treatment of cancer in the brain of said mammal, more particularly for the treatment of cancer in the human body, i. e. the brain. Such delivery of anticancer agents to the human brain was very difficult in the prior art, what concerns the effective amounts which could be provided to the site of action of the chemotherapeutic agent; surprisingly, the use of the present invention provides an effective and controllable amount of such substance(s) at the site of their action in an easily administrable composition.

In accordance with the present invention, such a use of said nanoparticles is preferred, wherein said chemotherapeutic anticancer agent is selected from the group consisting of alkylating agents, antimetabolites, natural anticancer products, hormones, metal co-ordination complexes and mixtures thereof. There is no restriction concerning the administration of substances of one single group or of more than one of the above groups which, of course, include numerous substances specifically mentioned above. There is only the requirement that these substances may be suitably incorporated into or adsorbed onto or absorbed by said nanoparticles used in the present invention and do not interfere with each other during such a use.

As specific substances for a use in accordance with a preferred embodiment of the invention, there may be mentioned the following substances, without restricting the inventive use to the substances mentioned below:

- nitrogen mustards, e. g. Cyclophosphamide, Trofosfamide, Ifosfamide and Chlorambucil;
- nitroso ureas, e. g. Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU) and Nimustine (ACNU);
- ethylene imines and methyl-melamines, e. g. Thiotepa;
- folic acid analogs, e. g. Methotrexate;
- pyrimidine analogs, e. g. 5-Fluorouracil and Cytarabine;
- purine analogs, e. g. Mercaptopurine and Azathioprine;
- vinca alkaloids, e. g. Vinblastine, Vincristine and Vindesine;
- epipodophyllotoxins, e. g. Etoposide and Teniposide;
- antibiotics, e. g. Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Bleomycin A2, Mitomycin C and Mitoxantrone;
- estrogens, e. g. Diethyl stilbestrol;
- gonadotropin-releasing hormon analogs, e. g. Leuprolide, Buserelin and Goserelin;
- antiestrogens, e. g. Tamoxifen and Aminoglutethimide;
- androgens, e. g. Testolactone and Drostanolonproprionate; and
- platinum complexes, e. g. Cisplatin and Carboplatin.

According to the invention, mixtures of the above substances may also be used as long as they result into a successful treatment of cancer, particularly of brain cancer, in mammals as for example in humans. Particularly preferred in the use of the nanoparticles of the püresent invention are Doxorubicin and/or Mitoxantrone, since the administration of any of these substances by using nanoparticles results into a successful anticancer treatment, particularly a successful treatment of brain tumors in mammals as for example in humans. In particular, a passage of the bbb by said substance in a therapeutically effective amount was observed, which fact was completely surprising for a skilled person being familiar with the prior art problem of providing a therapeutically effective amount of said anticancer agents in the brain.

A critical component of the nanoparticles used in the present invention is/are the stabilizer(s). In a preferred use, only one stabilizer is used whereby a passage of the bbb by said nanoparticles loaded with the anticancer drugs can be afforded in a successful way, and the anticancer drugs in said nanoparticles are directed to the tumor site in the brain in a high concentration. This was not yet possible in the prior art approaches. As a result thereof, the treatment of brain cancers could be considerably improved, and the success rates of the treatment could be increased as well.

The other critical component of the nanoparticles used in the present invention are the surfactant materials of the coating which materials are belonging to the same group of compounds as the above. The stabilizer may be present in the nanoparticles used in accordance with the present invention as a result of the manufacturing steps either in small remaining amounts or may form the coating allowing the passage of the effective substance(s) across the bbb. As an alternative, the separate coating may be provided. As a result, the outside wall of the nanoparticles used in the present invention is coated with the material allowing the passage of the bbb in a surprising manner. The application of the coating or the provision of the stabilizer in such nanoparticles is basically described in the above-mentioned International Patent Applications the disclosures of which are incorporated herein by reference.

In a preferred embodiment of the present inventive use, the material(s) of the stabilizer/ surfactant is/are selected selected from the group consisting of stabilizers/surfactants which allow a passage of said nanoparticles including said physiologically effective substance(s) across the blood brain barrier in said mammal and stabilizers/surfactants which allow a release of said physiologically effective substance(s) from said nanoparticles and a passage of said substance(s) across the blood brain barrier separate from said nanoparticles. It is furthermore preferred that said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbates, dextrans, carboxylic acid esters of multifunctional

alcohols, polyoxamers, polyoxamines, alkoxylated ethers, alkoxylated esters, alkoxylated mono-, di- and triglycerides, alkoxylated phenols and diphenols, substances of the Genapol [R] and Bauki [R] series, metal salts of carboxylic acids, metal salts of alcohol sulfates, and metal salts of sulfosuccinates and mixtures of two or more of said substances.

Specific examples of said stabilizers and/or surfactants which are used for the coating for the nanoparticles are mentioned below, without restricting the invention to the compounds or groups of compounds mentioned below. Preferably, said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbate 81, polysorbate 85, dextran 12.000, dextran 70,000, fatty acid esters of glycerol and sorbitol as glycerol monostearate, sorbitan monostearate and sorbitan monooleate, polyoxamer 188 (Pluronic R F68), ethoxylated ethers, ethoxylated esters, ethoxylated triglycerides, ethoxylated phenols and diphenols, metal salts of fatty acids and of fatty alcohol sulfates, more preferably the sodium salts of fatty acids and of fatty alcohol sulfates, even more preferably sodium stearate and sodium lauryl sulfate, and mixtures of two or more of said substances.

The most preferred stabilizers/surfactant materials are selected from the group consisting of polysorbate 80, polysorbate 85, dextran 12,000 or dextran 70,000 and mixtures thereof and mixtures of said stabilizers with other stabilizers. With the latter compounds, a superior use of the nanoparticles in the anticancer treatment can be achieved, particularly in the treatment of brain cancers in humans.

It is an accordance with a further preferred use of the nanoparticles, if said carrier and/or diluent which is used for the administration of the nanoparticles used in the present invention is/are selected from the group consisting of water, physiologically acceptable aqueous solutions containing salts and/or buffers and any other solution acceptable for administration to a mammal.

In accordance with the invention, there are further provided nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, for the treatment of cancer in said mammal.

In another aspect of the invention, there is provided a process for the treatment of cancer, particularly of brain cancer, in mammals, said process comprising the step of administering to said mammals nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, in an amount effective for the treatment of cancer.

In a preferred process according to the invention, the administration is an i.v. administration. It is particularly preferred that the treatment is a treatment of brain cancer, e. g. in mammals as for example humans.

The invention is further exemplified by the subsequent example which, however, should not be understood to limit the invention.

The anti-tumor effect of doxorubicin preparations was tested in rats with an intracranially transplanted glioblastoma 101/8. This tumor is known to have a substantial number of receptors to the epidermal growth factor.

The animals were treated with 1.5 mg/kg x 3 of doxorubicin which makes a total course dose of 4.5 mg/kg (the total dose for mice is usually 7 to 8 mg/kg).

The drugs were administered i/v on the day 2 (48 h after implantation of the tumor), day 5 and day 8 after tumor implantation.

The experiment was started on 9 to 13 December 1998 and was not yet completed by 20 May 1999 since some of the animals are still alive.

Drug preparations were administered as usual in saline or in 1 % Tween ^{R} 80 . For the coating of the nanoparticles loaded with doxorubicin, the suspension was added with 1 % Tween ^{R} 80 with stirring. The mixture was incubated for 2 h.

It can be seen from the subsequent tables that in the case that doxorubicin was administered ("Dox"), the rats died after the times (hours, h) given in column 1 of the upper table. In the case of the administration of the drug with Tween 80, most of the rats died, too. As in the first case, all rats died after administration of Tween 80 coated nanoparticles and doxorubicin-loaded nanoparticles without coating (columns 3 and 4 of the upper table). Only in the case that doxorubicin-loaded nanoparticles were coated with Tween 80, 3 of 8 rats survived.

This result clearly shows that the surfactant-coated nanoparticles were suitable to promote the passage of an effective dose of the anticancer agent doxorubicin across the bbb for a successful anticancer treatment.

Survival rate (days) of glioblastoma 101/8 bearing rats after i/v administration of doxorubicin preparations

Control	Dox	Dox + Tween 80	NP + Tween 80	Dox-NP	Dox-NP + Tween 80
9	11	13	9	13	22
11	13	13	11	13	22
12	14	23	11	15	22
13	14	38	12	15	23
13	14	51	18	17	37
13	15	alive	19	38	alive
14	20			40	alive
17	21			50	alive
17	23				

Group	Median survival time (MST, days)	Prolongation of MST %	Survivals (by day 60)
Control	13,2		
Dox	16,1	22	0/9
Dox-NP	25,1	90	0/8
Dox + Tween	27,6	112	1/6
Dox-NP + Tween	25,1+	91	3/8
NP + Tween	13,3	0	0/6

Claims

1. Use of nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, for the manufacture of a medicament for the treatment of cancer in said mammal.

2. The use according to claim 1 for the treatment of brain cancer in said mammal.

3. The use according to claim 1 or claim 2, wherein said nanoparticles comprise particles of said polymeric material having a diameter of below 1,000 nm, preferably of from 1 to 1,000 nm.

4. The use according to any of the claims 1 to 3, wherein said polymeric material is selected from the group consisting of polyacrylates, polymethacrylates, polycyanoacrylates, polyacrylamides, polylactates, polyglycolates, polyanhydrates, polyorthoesters, gelatin, polysaccharides, albumin, polystyrenes, polyvinyls, polyacroöein, polyglutaraldehydes and derivatives, copolymers and mixtures thereof.

5. The use according to any of the claims 1 to 4, wherein said nanoparticles comprise said physiologically effective substance(s) to be delivered to said mammal in the form adsorbed, absorbed and/or incorporated thereto.

6. The use according to any of the claims 1 to 5, wherein said physiologically effective substance(s) to be delivered to said mammal comprise(s) one or more chemotherapeutic agent(s) for the cancer treatment, preferably alkylating agents, antimetabolites, natural anticancer products, hormones, metal co-ordination complexes and mixtures thereof, more preferably nitrogen mustards, nitroso ureas, ethylene imines and methyl-melamines, folic acid analogs, pyrimidine analogs, purine analogs, vinca alkaloids, epipodophyllotoxins, antibiotics, estrogens, gonadotropin-releasing hormon analogs, antiestrogens, androgens, platinum complexes and mixtures thereof, even more preferred doxorubicin and/or mitoxantrone.

7. The use according to any of the claims 1 to 6, wherein the stabilizer and/or surfactant coating material is selected from the group consisting of stabilizers/surfactants which allow a passage of said nanoparticles including said physiologically effective substance(s) across the blood brain barrier in said mammal and stabilizers/surfactants which allow a release of said physiologically effective substance(s) from said nanoparticles and a passage of said substance(s) across the blood brain barrier separate from said nanoparticles, preferably wherein said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbates, dextrans, carboxylic acid esters of multifunctional alcohols, polyoxamers, polyoxamines, alkoxylated ethers, alkoxylated esters, alkoxylated mono-, di- and triglycerides, alkoxylated phenols and diphenols, substances of the Genapol ^{R} and Bauki ^{R} series, metal salts of carboxylic acids, metal salts of alcohol sulfates, and metal salts of sulfosuccinates and mixtures of two or more of said substances, more preferably wherein said stabilizer/surfactant comprises a substance selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbate 81, polysorbate 85, dextran 12.000, dextran 70,000, fatty acid esters of glycerol and sorbitol as glycerol monostearate, sorbitan monostearate and sorbitan monooleate, polyoxamer 188 (Pluronic R F68), ethoxylated ethers, ethoxylated esters, ethoxylated triglycerides, ethoxylated phenols

and diphenols, metal salts of fatty acids and of fatty alcohol sulfates, more preferably the sodium salts of fatty acids and of fatty alcohol sulfates, even more preferably sodium stearate and sodium lauryl sulfate, and mixtures of two or more of said substances, even more preferably polysorbate 80, polysorbate 85, dextran 12,000 or dextran 70,000 and mixtures thereof and mixtures of the stabilizers/surfactants with other stabilizers/surfactants.

8. The use according to any of the claims 1 to 7, wherein said carrier and/or diluent is/are selected from the group consisting of water, physiologically acceptable aqueous solutions containing salts and/or buffers and any other solution acceptable for administration to a mammal.

9. The use according to any of the claims 1 to 8, wherein the administration is an i. v. administration.

10. The use according to any of the claims 1 to 9, wherein said mammal is a human.

11. Nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, for the treatment of cancer in said mammal.

12. A process for the treatment of cancer, particularly of brain cancer, in mammals, said process comprising the step of administering to said mammals nanoparticles made of a polymeric material, said nanoparticles comprising said polymeric material, one or more substance(s) physiologically effective in the treatment of cancer upon delivery to a

mammal, one or more stabilizer(s) for said nanoparticles allowing targeting of said physiologically effective substance(s) to a specific site within said mammalian body and/or a surfactant coating on said nanoparticles, said nanoparticles optionally being provided within a physiologically acceptable carrier and/or diluent allowing the delivery of said nanoparticles to the target within said mammal after administration, in an amount effective for the treatment of cancer.

13. The process of claim 12, wherein the administration is an i.v. or i.p. administration.

14. The process according to claim 12 or claim 13, wherein the treatment is a treatment of brain cancer.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/EP 99/03838

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/51 A61K31/70 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 22963 A (MEDINOVA MED CONSULTING GMBH) 31 August 1995 (1995-08-31) cited in the application the whole document in particular: page 6, line 10 -page 7 page 13, line 9 - line 11	1-14
X	WO 98 56361 A (MEDINOVA MED CONSULTING GMBH ;SABEL BERNHARD A (DE); SCHROEDER ULR) 17 December 1998 (1998-12-17) cited in the application the whole document in particular: page 5, line 20 -page 9, line 5 page 15, line 1 - line 3	1-14

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X Further documents are listed in the continuation of box C.

X Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 February 2000	24/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Epskamp, S

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 99/03838

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 45 950 A (DDS DRUG DELIVERY SERVICE GES) 22 April 1999 (1999-04-22) page 3, line 27 -page 4, line 9 page 5, line 40 - line 45; examples 2,6; table 1 page 9, line 10 - line 26 claims 1-20	1-14
X	RESZKA R, ET AL.: "Body distribution of free, liposomal and nanoparticle-associated mitoxantrone in B16-melanoma-bearing mice" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 'Online! vol. 280, no. 1, 1997, pages 232-237, XP002129865 ISSN 0022-3565 Retrieved from the Internet: <URL:http://jpet.aspetjournals.org/cgi/reprint/280/1/232> 'retrieved on 2000-02-07! page 233, line 31 - line 49 page 233, line 57 -page 234, line 21 page 236, line 12 - line 27; figures 1-6; table 1	1,3-13
X	US 5 133 908 A (STAINMESSE SERGE ET AL) 28 July 1992 (1992-07-28) column 2, line 27 -column 3, line 45 column 5 -column 7; examples 1,6,7 column 9, line 54 -column 10, line 8	1,3-13
X	COUVREUR P, ET AL.: "Toxicity of polyalkylcyanoacrylate nanoparticles II: doxorubicin-loaded nanoparticles" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 71, no. 7, 1982, pages 790-792, XP000783921 ISSN 0022-3549 page 790, right-hand column, line 4 -page 791, left-hand column, line 12	1,3-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/ 03838

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/EP 99/03838

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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